182. *The Reaction between Hydrazine Hydrate and 4-Chloroquinoline Derivatives.*

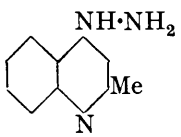
By O. G. Backeberg and C. A. Friedmann.

Koenigs and von Loesch showed that the product of the reaction between hydrazine hydrate and 4-chloroquinaldine was either 4-hydrazinoquinaldine (I) or an isomeric substance of unknown constitution, according to the conditions of the reaction. This isomer has been shown to be 3 : 4-*diaminoquinaldine* (V). Although this compound could not be prepared by direct synthesis for comparison, the procedure adopted, which involved the preparation of a number of methyl-substituted similar compounds, nevertheless established its constitution. Furthermore, its *o*-diamine structure was indicated by the fact that it formed a *diacetyl* derivative convertible into a *quiniminazole*.

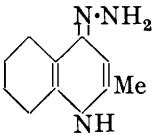
For the attempted synthesis of 3 : 4-diaminoquinaldine, it was necessary to prepare 3 : 4-*dichloroquinaldine*; this compound proved to be entirely different from the compound of that name described by von Braun and Heymons in 1930. An attempt was also made to synthesise the diamine by nitrating 4-aminoquinaldine, but the first isolable product was a *nitro*-4-*nitroaminoquinaldine*, and it was not found possible to introduce one nitro-group only into 4-aminoquinaldine.

Koenigs and von Loesch (*J. pr. Chem.*, 1935, **143**, 59) found that two entirely different products were obtained from the interaction between hydrazine hydrate and 4-chloroquinaldine according to the conditions employed : the normal reaction, resulting in the expected 4-hydrazinoquinaldine (I), m. p. 200°, took place in alcoholic solution on the water-bath, whereas in a sealed tube at 150° the product was a substance (II), m. p. 122°. The latter substance was first prepared by Marckwald and Chain (*Ber.*, 1900, **33**, 1898), who

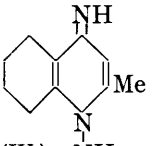
thought that it was in fact the hydrazine (I). Koenigs and von Loesch referred to it as a diamine and reported that it was different from 3 : 4- and 4 : 5-diaminoquinaldine, which they prepared for comparison, but they did not describe the properties or the methods of preparation.



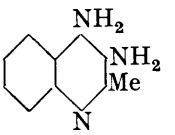
(I.)



(III.)



(IV.)

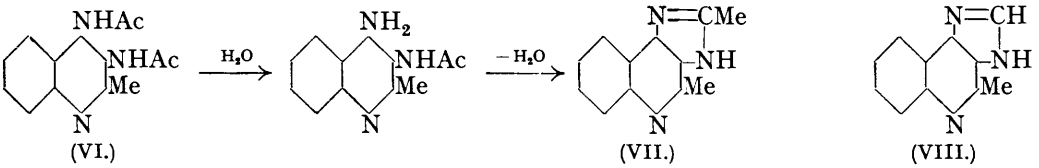


(V.)

The purpose of the present investigation was to establish the constitution of Marckwald and Chain's product. Molecular-weight determinations and analysis confirmed the fact that the compound is $C_{10}H_{11}N_3$ (II), isomeric with (I). The absorption spectra of the two compounds, taken with a Hilger quartz spectrograph (E. 31), indicate a close relationship between them; there is a slight difference in the positions of the two bands, and in the case of the hydrazine (I) considerable absorption occurs in the visible region, but nevertheless the two bands are similar in shape. Furthermore, the hydrazine (I) could be transformed into the isomer (II) by heating it in a sealed tube with hydrazine hydrate; this appears to indicate that the hydrazine (I) is the first product of the reaction and, by analogy with the conversion of phenylhydrazine into *p*-phenylenediamine (Thiele and Wheeler, *Ber.*, 1895, **28**, 1538), the transformation involves the conversion of a 4-hydrazino-group into two amino-groups, of which one must be in the 4-position. The stability in air of the compound (II) makes a diamine structure improbable; yet, apart from the possibility of tautomerism, such as is indicated by (III), or of a compound of the form (IV)—actually both of these are excluded by the fact that such compounds would form 4-aminoquinaldine on reduction, whereas (II) is unchanged—a diamine structure appears to be the only alternative, and this means that (II) must be 3 : 4-, 4 : 5-, 4 : 6-, 4 : 7-, or 4 : 8-diaminoquinaldine. Of these, the 3 : 4-compound is mentioned by Conrad and Limpach (*Ber.*, 1888, **21**, 1983), who obtained a hydrochloride which they did not describe, and attempts to prepare the diamine by their method were unsuccessful; the 4 : 6- and the 4 : 8-diamine were described by Jensch (D.R.-P. 591,480) as having m. p. 197° and 168° respectively, but it has not been found possible to prepare them by the method referred to (compare Backeberg, J., 1935, 1568).

Owing to the difficulties encountered in attempting direct syntheses of these various diamines, a different procedure was adopted to elucidate the structure of (II). In the conversion of (I) into (II) an amino-group must migrate to the position 3, 5, 6, 7, or 8, and these were each in turn blocked by a methyl group in the appropriate 4-chloroquinaldine derivative, so that, if a sealed-tube product was obtained which resembled Marckwald and Chain's isomer (II), the assumption was made that the position blocked by the methyl group was not involved in the transformation. The result of this procedure showed that 6-methyl-, 5(or 7)-methyl-, 8-methyl-, 5 : 7-dimethyl-, 6 : 8-dimethyl-4-chloroquinaldine, as well as 4-chloroquinoline, all reacted with hydrazine hydrate in a sealed tube to give a stable product which was not a hydrazine, and which therefore corresponded to Marckwald and Chain's compound (II). In the case of 4-chloro-3-methylquinaldine no reaction occurred in alcoholic solution on the water-bath even after 50 hours, or in a sealed tube under the conditions specified, but if after 10 hours at 150° the temperature was raised to 200° for a further 10 hours, although some of the chloro-compound was still unchanged, ammonia was formed and a gummy substance was obtained from which it was not found possible to isolate any crystalline material. This failure to react with hydrazine hydrate did not appear to be due to steric hindrance, since the chloro-compound reacted normally with aniline. The conclusion to be drawn is that Marckwald and Chain's isomer (II) is in fact 3 : 4-*diaminoquinaldine* (V); further, that the sealed-tube products obtained from 6-methyl-, 5(or 7)-methyl-, 8-methyl-, 5 : 7-dimethyl-, and 6 : 8-dimethyl-4-chloroquinaldine, as well as 4-chloroquinoline, are the corresponding 3 : 4-diamino-compounds.

The compound (V) is not, however, a normal *o*-diamine, for it was not found possible to condense it with diacetyl, benzil or phenanthraquinone. With acetic anhydride a *diacetyl* derivative (VI) was readily obtained, which is further evidence for the presence of two amino-groups in (II); this diacetyl derivative was easily changed, by warming for a short time in alcohol–hydrochloric acid solution, into a compound $C_{12}H_{11}N_3$, which is regarded as 2 : 2′-*dimethylquin*(3 : 4 : 5′ : 4′)*iminazole* (VII):



(VI.) (VII.) (VIII.)

The same iminazole (VII) was formed by refluxing the isomer (II) with acetic acid, and 2-*methylquin*(3 : 4 : 5′ : 4′)*iminazole* (VIII) was readily obtained by the action of formic acid on the compound (II). This formation of an iminazole is regarded as strong confirmatory evidence for the *o*-diamine structure of (II). The iminazole (VII) has the interesting property of being less soluble in hot than in cold dilute methyl or ethyl alcohol.

Attempts to synthese 3 : 4-diaminoquinaldine (V) by the action of ammonia on 3 : 4-*dichloroquinaldine* and by the nitration of 4-aminoquinaldine were unsuccessful. The dichloro-derivative required for the first method was described by von Braun and Heymons (*Ber.*, 1930, **63**, 3197) as having m. p. 322°, although 4-chloroquinoline derivatives are all characterised by comparatively low melting points. The compound was prepared by a method slightly different from that of the above authors and was found to have m. p. 67°; its identity was confirmed by conversion into the known 3-chloro-4-anilinoquinaldine. The second method was an attempt to apply the procedure employed by Koenigs, Kinne, and Weiss (*Ber.*, 1924, **57**, 1177) for the preparation of 3-nitro-4-aminopyridine to the case of 4-aminoquinaldine, but the most carefully controlled nitration yielded 4-*nitroamino-nitroquinaldine* and it was not found possible to introduce only a single nitro-group into 4-aminoquinaldine.

In the reactions on the water-bath of the various 4-chloroquinoline derivatives mentioned, in only one case, namely, from 4-chloro-8-methylquinaldine, was the corresponding hydrazine obtained; furthermore, in the sealed-tube reactions, it was observed that, if the temperature was raised appreciably above 150°, there was a tendency for a side reaction to take place in which an azo-compound was formed, and in one instance, from 4-*chloro*-5 : 7-*dimethylquinaldine*, the *azo*-compound was isolated and analysed. Otherwise attention was mainly focused on obtaining a sealed-tube product corresponding to Marckwald and Chain's isomer (II).

Experimental.

The experimental conditions for the interaction of 4-chloroquinoline derivatives and hydrazine hydrate were those employed by Koenigs and von Loesch (*loc. cit.*); unless otherwise stated, the sealed-tube reaction was carried out at 150° for 5 hours. The sealed-tube reaction products all possessed similar properties; like the compound (II), they were stable in air, did not reduce Fehling's solution, and were unchanged by copper sulphate in acid solution.

Marckwald and Chain's isomer (II), *i.e.*, 3 : 4-*diaminoquinaldine* (V), crystallised from hot water (charcoal) in colourless plates, m. p. 122° [Found: C, 69·4; H, 6·6; *M* (ebullioscopic in acetone), 174. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·35%; *M*, 173]. The *chloroplatinate* formed purple needles, decomp. above 300° (Found: Pt, 36·9. $2C_{10}H_{11}N_3,3H_2PtCl_6$ requires Pt, 37·1%).

The compound (II) was recovered unchanged when reduction was attempted with zinc dust and hydrochloric acid, or with red phosphorus and hydriodic acid (compare Ephraim, *Ber.*, 1892, **25**, 2707; 1893, **26**, 2227).

3 : 4-*Diacetamidoquinaldine* (VI), obtained when an acetic acid solution of the base (II) was boiled for a few minutes with acetic anhydride, formed colourless needles, m. p. 193° after recrystallisation from alcohol [Found: C, 65·4; H, 5·9; *M* (Rast), 256. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·8%; *M*, 257].

2 : 2′-*Dimethylquin*(3 : 4 : 5′ : 4′)*iminazole* (VII).—An alcoholic solution of the diacetyl derivative (VI) was boiled for a few minutes with a little concentrated hydrochloric acid, diluted with water, and made alkaline; the white solid obtained crystallised from hot water, in which it was sparingly soluble, in colourless needles, m. p. 100° (Found : C, 72·9; H, 5·65; N, 20·9. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·1%). This *quiniminazole* (VII) was also formed by refluxing the base (II) with glacial acetic acid for 1 hour. It was unchanged by heating at 100° for 2 hours with 75% sulphuric acid. Methyl or ethyl alcohol, just sufficient for solution, was added to a cold suspension of the iminazole (VII) in water; the base separated as an oil on boiling and redissolved on cooling. The *picrate* formed yellow needles, m. p. 200° (Found : N, 19·9. $C_{12}H_{11}N_3,C_6H_3O_7N_3$ requires N, 19·7%); it was also formed (m. p. and mixed m. p.) when the diacetyl derivative (VI) was warmed with an alcoholic solution of picric acid. The iminazole (VII) formed an orange-coloured *chloroplatinate*, which crystallised from alcoholic hydrochloric acid in small prisms, decomp. above 300° (Found : Pt, 24·3, *i.e.*, *M*, 195·5. $2C_{12}H_{11}N_3,H_2PtCl_6$ requires Pt, 24·25%, *i.e.*, *M*, 197).

2-*Methylquin*(3 : 4 : 5′ : 4′)*iminazole* (VIII).—The base (II) was refluxed for 1 hour with anhydrous formic acid, diluted with water, and made alkaline. The solid which separated crystallised from dilute methyl alcohol in fine colourless needles, m. p. 97° (Found : N, 22·9. $C_{11}H_9N_3$ requires N, 22·95%). The *picrate* formed yellow needles, m. p. 210° (Found : N, 20·1. $C_{11}H_9N_3,C_6H_3O_7N_3$ requires N, 20·4%).

Conversion of 4-*Hydrazinoquinaldine* (I) *into the Isomer* (II).—1 G. of 4-hydrazinoquinaldine (I) was heated with 3 c.c. of hydrazine hydrate in a sealed tube at 150° for 5 hours and then for a further 5 hours at 200°. The product crystallised from water in colourless plates, m. p. 122°, alone or mixed with the compound (II) prepared by Marckwald and Chain's method (*loc. cit.*).

4-*Hydrazino*-8-*methylquinaldine* crystallised from alcohol in white plates, m. p. 199° (Found : N, 22·3. $C_{11}H_{13}N_3$ requires N, 22·5%). The substance was unstable in air and gradually turned brown; it reduced Fehling's solution. When it was heated with copper sulphate in acid solution, and the mixture made alkaline, an odour of quinoline was detected. It formed a sparingly soluble sulphate, m. p. 289° (decomp.).

3 : 4-*Diamino*-8-*methylquinaldine* formed small colourless prisms, m. p. 122°, from hot water (Found : N, 22·5. $C_{11}H_{13}N_3$ requires N, 22·5%). The *picrate* had m. p. 202° (Found : N, 19·95. $C_{11}H_{13}N_3,C_6H_3O_7N_3$ requires N, 20·0%).

3 : 4-*Diamino*-6-*methylquinaldine* formed colourless needles, m. p. 153°, from dilute alcohol (Found : N, 22·1%). The *picrate* had m. p. 208° (decomp.) (Found : N, 20·1%).

4-*Hydroxy*-5(*or* 7)-*methylquinaldine* was prepared in the usual way from *m*-toluidine and ethyl acetoacetate. The crude product was dissolved in hot dilute caustic soda solution and filtered; on cooling, a pale yellow solid separated, which crystallised from hot water in colourless plates, m. p. 255—270°. This product was apparently a mixture of 5- and 7-methyl-4-hydroxyquinaldine. Repeated crystallisation from dilute methyl alcohol gave a product, m. p. 273° (Found : C, 76·3; H, 6·3. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·35%). On distillation with zinc dust, a small quantity of an oil, soluble in acids and having an odour of quinoline, was obtained; it formed a picrate, m. p. 262°. Reference to the literature indicated that there is some difference of opinion as to whether the product obtained from *m*-toluidine by the Doebner–Miller synthesis is 5- or 7-methylquinaldine, and a picrate of the base is not described. Doebner and von Miller (*Ber.*, 1883, **16**, 2471) refer to the compound as *m*-methylquinaldine; so also does Rist (*Ber.*, 1890, **23**, 3483), but Decker and Remfry (*Ber.*, 1905, **38**, 2775) consider that Rist interpreted his experimental results incorrectly, and that the compound is 5-methylquinaldine.

4-*Chloro*-5(*or* 7)-*methylquinaldine*, prepared from the above 4-hydroxy-compound by the action of phosphoryl chloride, was purified by steam distillation; it crystallised from dilute alcohol in colourless needles, m. p. 78° (Found : N, 7·6. $C_{11}H_{10}NCl$ requires N, 7·4%). The *picrate* had m. p. 193° (Found : N, 14·0. $C_{11}H_{10}NCl,C_6H_3O_7N_3$ requires N, 13·8%).

3 : 4-*Diamino*-5(*or* 7)-*methylquinaldine* formed colourless needles, m. p. 150° from dilute alcohol (Found : N, 22·5. $C_{11}H_{13}N_3$ requires N, 22·5%). The *picrate* had m. p. 212° (decomp.) (Found : N, 20·4. $C_{11}H_{13}N_3,C_6H_3O_7N_3$ requires N, 20·0%).

3 : 4-*Diamino*-6 : 8-*dimethylquinaldine*, prepared in a sealed tube at 150° (10 hours) and at 180° (further 10 hours), crystallised from dilute alcohol in colourless needles, m. p. 140° (Found : N, 21·3. $C_{12}H_{15}N_3$ requires N, 21·4%). The *picrate* had m. p. 183° (Found : N, 19·4. $C_{12}H_{15}N_3,C_6H_3O_7N_3$ requires N, 19·5%).

5 : 7-*Dimethyl*-4-*hydroxyquinaldine*.—The 1 : 3 : 5-xylidine required was prepared from 1 : 3 : 4-xylidine by acetylation, nitration, deacetylation, diazotisation of the sulphate with

methyl nitrite, and reduction with ethyl alcohol; the 1 : 3 : 5-nitroxylene so obtained was reduced with iron filings and acetic acid. In this way 90 g. of 1 : 3 : 4-xylidine yielded 25 g. of 1 : 3 : 5-xylidine. The base was condensed with ethyl acetoacetate in the usual way, and converted into 5 : 7-*dimethyl*-4-*hydroxyquinaldine* which crystallised from dilute alcohol in colourless needles, m. p. 288° (decomp.) (Found : N, 7·5. $C_{12}H_{13}ON$ requires N, 7·5%). *Picrate*, m. p. 207° (Found : N, 13·6. $C_{12}H_{13}ON,C_6H_3O_7N_3$ requires N, 13·5%).

4-*Chloro*-5 : 7-*dimethylquinaldine*, prepared from the above 4-hydroxy-compound by the action of phosphoryl chloride, crystallised from dilute alcohol in colourless needles, m. p. 73° (Found : N, 6·85. $C_{12}H_{12}NCl$ requires N, 6·8%). The *picrate* had m. p. 226° (Found : N, 12·6. $C_{12}H_{12}NCl,C_6H_3O_7N_3$ requires N, 12·9%).

3 : 4-*Diamino*-5 : 7-*dimethylquinaldine* was prepared in a sealed tube at 170° (8 hours). The product was washed with water, dissolved in dilute acetic acid, and filtered, and the filtrate made alkaline with ammonia. The product, which consisted of a mixture of the diamine and the azo-compound, was separated into its constituents by extraction with hot water, from which the diamine crystallised in colourless needles, m. p. 150° (Found : N, 21·5. $C_{12}H_{15}N_3$ requires N, 21·4%). The *picrate* had m. p. 214° (Found : N, 19·5. $C_{12}H_{15}N_3,C_6H_3O_7N_3$ requires N, 19·5%).

The brown residue from the above extraction, insoluble in water, was crystallised from alcohol, in which it was sparingly soluble, 4 : 4′-*azo*-5 : 7 : 5′ : 7′-*tetramethylquinaldine* separating in brown needles, m. p. 250° (decomp.) (Found : N, 15·3. $C_{24}H_{24}N_4$ requires N, 15·2%).

3 : 4-*Diaminoquinoline* crystallised from dilute alcohol in colourless plates, m. p. 129° (Found : N, 26·55. $C_9H_9N_3$ requires N, 26·4%). The *picrate* had m. p. 197° (Found : N, 21·9. $C_9H_9N_3,C_6H_3O_7N_3$ requires N, 21·75%). Brydówna (*Rocz. Chem.*, 1932, **12**, 89) described a product from 4-chloroquinoline and hydrazine hydrate, m. p. 140—142°; the original literature not being available, it has not been found possible to ascertain the conditions employed by him for the reaction.

4-Chloro-3-methylquinaldine was readily converted into 4-*anilino*-3-*methylquinaldine* (compare Backeberg, J., 1932, 1984) in quantitative yield; this product crystallised from alcohol in colourless needles, m. p. 219° (Found : N, 11·6. $C_{17}H_{16}N_2$ requires N, 11·3%).

3 : 4-*Dichloroquinaldine*.—70 G. of 3-chloro-4-anilino-2-chloromethylquinoline (von Braun and Heymons, *loc. cit.*) were dissolved in excess of glacial acetic acid, and excess of zinc dust added. The mixture was refluxed for 1 hour, the bulk of the acetic acid removed by distillation after the excess of zinc had been filtered off, and the residue diluted with water and made alkaline with excess of caustic soda; 3-chloro-4-anilinoquinaldine, m. p. 172°, was thus obtained in good yield. 5 G. of this compound and 20 c.c. of fuming hydrochloric acid were heated in a sealed tube at 180° for 8 hours. The resulting brown liquid was evaporated to dryness on the water-bath, and the residue made alkaline and steam-distilled to remove a small quantity of 3 : 4-dichloroquinaldine. The residual liquid was filtered and neutralised; 3 g. of 3-*chloro*-4-*hydroxyquinaldine* then separated as a pale yellow solid, m. p. 340° after crystallisation from methyl alcohol (Found : C, 61·8; H, 4·4. $C_{10}H_8ONCl$ requires C, 62·0; H, 4·1%). 11 G. of the crude hydroxy-compound were refluxed with excess of phosphoryl chloride for 1 hour and the resulting solution was poured gradually with cooling into water, made alkaline with 50% caustic soda solution, and steam-distilled; the 3 : 4-*dichloroquinaldine* (6 g.) obtained crystallised from dilute alcohol in colourless needles, m. p. 67° (Found : C, 56·5; H, 3·5; Cl, 33·1. $C_{10}H_7NCl_2$ requires C, 56·6; H, 3·3; Cl, 33·5%). An appreciable quantity of a high-melting solid, non-volatile in steam, was formed as a by-product, which was not further investigated. For further identification 3 : 4-dichloroquinaldine was converted into 3-chloro-4-anilinoquinaldine, m. p. 172° (see above). Numerous attempts to convert the dichloro-compound into 3 : 4-diaminoquinaldine were unsuccessful (compare Ashley, Browning, Cohen, and Gulbransen, *Proc. Roy. Soc.*, 1933, *B*, **113**, 295; Das-Gupta, *J. Indian Chem. Soc.*, 1933, **10**, 114; Maier-Bode, *Ber.*, 1936, **69**, 1534).

Nitration of 4-*Aminoquinaldine* (compare Koenigs, Kinne, and Weiss, *loc. cit.*).—6 G. of 4-aminoquinaldine were dissolved in 30 g. of concentrated sulphuric acid, with gentle warming if necessary. The solution was cooled in a freezing mixture (the sulphate of the amine separated) and stirred vigorously, and 5 c.c. of nitric acid (*d* 1·52) added drop by drop; the sulphate gradually dissolved to give a dark red solution. Stirring was continued for 1 hour, the temperature being kept below 0°; the solution was then poured on ice. An orange-coloured solid separated, which was filtered off and washed; it crystallised from alcohol, in which it was sparingly soluble, in yellow needles, which decomposed explosively at 200° without previous melting. This product was 4-*nitroaminonitroquinaldine* (Found : N, 22·1. $C_{10}H_8O_4N_4$ requires N, 22·6%).

On reduction with zinc and dilute sulphuric acid and neutralisation, a solution was obtained which reduced Fehling's solution, owing to the formation of a hydrazine by the reduction of the nitroamine.

When the filtrate from the nitroamine was neutralised, a gelatinous mass separated, which crystallised from alcohol in yellow plates, m. p. 276°. This was *dinitro-4-aminoquinaldine* (Found: C, 48·9; H, 3·6; N, 22·3. $C_{10}H_8O_4N_4$ requires C, 48·4; H, 3·2; N, 22·6%). The same dinitro-4-amino-compound was obtained when the above nitroamine was dissolved in small portions at a time in concentrated sulphuric acid at 0°, and the solution gradually warmed to 50°, cooled, poured on ice, and neutralised. The dinitro-compound only was obtained if, after nitration as described as above, the solution was allowed to reach room temperature and then poured on ice.

The reduction of dinitro-4-aminoquinaldine was carried out (a) with sodium sulphide (compare Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690), a brown product, m. p. 220° (decomp.), being obtained, which appears to be *4-aminonitroaminoquinaldine* (Found: N, 26·1. $C_{10}H_{10}O_2N_4$ requires N, 25·7%); (b) with tin and hydrochloric acid. The tin was removed with hydrogen sulphide, and the resulting solution evaporated to dryness on the water-bath; the resulting hydrochloride crystallised from concentrated hydrochloric acid in brown needles, m. p. 293°. It has not been found possible to assign a structure to this compound, which dissolved readily in water with an intense blue fluorescence; the free base could not be isolated from it (Found: C, 38·2; H, 5·3; ionisable Cl, 22·9, 22·6%).

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